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REFERENCES:
2. EU SMP C, Jul 2010.
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Introduction

Chronic obstructive pulmonary disease (COPD) is associated with significant morbidity and mortality, and is predicted to be the fourth leading cause of death worldwide by 2030.¹ In Asia, there is a high prevalence of COPD risk factors such as cigarette smoking and the use of biomass fuels.² The mean regional COPD prevalence rate for Asia is estimated to be 6.3%; this equates to 56.6 million moderate-to-severe cases of COPD among individuals aged 30 years and above.² However, there is a two-fold variation in COPD prevalence rates across the region. In Hong Kong, there are 139,000 cases of moderate-to-severe COPD in adults aged 30 years and above, which equates to a prevalence rate of 3.5%.²

Exacerbations in COPD

COPD is a progressive disease characterized by persistent airway and systemic inflammation. Inflammatory cells, such as neutrophils and macrophages, accumulate in the lungs triggering an inflammatory cascade that leads to chronic airflow limitation and systemic inflammation.³ The natural course of COPD includes intermittent exacerbations – an acute worsening of symptoms – that further amplify the inflammation that is always present in the stable state.

Exacerbations contribute to a more rapid decline in lung function and subsequent reductions in quality of life (QoL).⁴ Exacerbations increase in frequency and severity as COPD progresses. However, a history of exacerbations is generally the most reliable predictor of future exacerbations – suggesting that there is an independent susceptibility phenotype that is influenced by the rate of exacerbations irrespective of disease state.⁴

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study (n=2,318), in adults aged 40 to 75 years with a history of ≥10 pack years of smoking, identified a frequent-exacerbation phenotype which appeared to be relatively stable over a period of 3 years. This phenotype could be predicted based on the patient’s recall of previous treated events, and was associated with more severe disease, prior exacerbations and a worse health-related QoL.⁴ (Table)

Patients who experience frequent exacerbations have a worse prognosis than patients with less frequent exacerbations, reinforcing the importance of exacerbation prevention in the management of patients with COPD. Furthermore, given the heterogeneous nature of COPD, a more individualized treatment approach may enhance treatment outcomes.⁵

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Number of exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 vs 0 (OR)</td>
</tr>
<tr>
<td>Exacerbation during previous year</td>
<td>2.24 (p&lt;0.001)</td>
</tr>
<tr>
<td>FEV₁ (per 100 mL decrease)</td>
<td>1.06 (p&lt;0.001)</td>
</tr>
<tr>
<td>SGRQ score (per increase of 4 points)</td>
<td>1.01</td>
</tr>
<tr>
<td>History of reflux or heartburn</td>
<td>1.61 (p&lt;0.001)</td>
</tr>
<tr>
<td>White-cell count (per increase of 1 x 10³/mm³)</td>
<td>1.02</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in 1 second; OR = odds ratio; SGRQ = St George’s Respiratory Questionnaire
Adapted from reference 4.
PDE4 Inhibitors Target COPD Inflammation

Current therapeutic options primarily treat the symptoms of COPD rather than targeting the underlying disease pathology. Therefore, many patients with COPD have suboptimal disease control. Anti-inflammatory therapy with inhaled corticosteroids has a modest effect on COPD, and despite improving lung function and reducing exacerbations in patients with severe COPD, it has little effect on disease progression.5

Phosphodiesterase-4 (PDE4) is the primary PDE isoenzyme found in cells involved in inflammatory airways diseases, such as COPD.5 A new class of agents – PDE4 inhibitors – has been developed specifically to target the inflammatory component of COPD. The first agent in this class to be approved for oral once-daily treatment of severe COPD is roflumilast.5 Roflumilast has high potency and selectivity for PDE4 without affecting other PDE isoenzymes found in various cells and tissues.

Preclinical studies demonstrate that roflumilast reduces the accumulation of neutrophils in bronchoalveolar lavage fluid following short-term exposure to tobacco smoke,5 decreases the production of mucus in inflamed lungs,6 decreases sputum in inflammatory cells,7 reduces alveolar destruction and may improve mucociliary clearance.8,9

“Current therapeutic options primarily treat the symptoms of COPD”

Roflumilast: The Clinical Evidence

The beneficial effects of roflumilast on lung function and quality of life have been demonstrated in patients with moderate-to-severe COPD.10-11 In 1,513 patients with severe stable COPD, oral roflumilast 500 μg plus inhaled corticosteroids produced a modest but significant improvement in lung function, which was evident after 4 weeks of treatment and maintained over a 1-year period (39 mL vs placebo; p=0.001).10 These findings were replicated in two multicenter studies in outpatients aged ≥40 years with moderate-to-severe COPD treated with the long-acting bronchodilators (LABA) salmeterol (M127 study; n=933) or tiotropium (M128 study; n=743).11 Consistent improvements in pre-bronchodilator FEV1 were reported with oral roflumilast 500 μg plus salmeterol (49 mL; p<0.0001) and oral roflumilast 500 μg plus tiotropium (80 mL; p<0.0001). (Figure 1A) Similar improvements were reported for post-bronchodilator FEV1 (Figure 1B) A post-hoc analysis of these studies reported a reduction in the mean annual moderate-to-severe exacerbation rate of 36.8% in the M127 study (p=0.0315) and 23.2% in the M128 study.

Two 1-year multicenter trials (M2-124 and M2-125) that enrolled more than 3,000 outpatients aged 40 years and above with severe airflow limitation, bronchitic symptoms and a history of exacerbations demonstrated significant reductions in exacerbation rates following treatment with roflumilast.12 In addition to improving lung function, roflumilast produced a 17% reduction in the rate of moderate-to-severe exacerbations (p=0.0003) and a 16% reduction in the total number of exacerbations requiring systemic corticosteroids or antibiotic treatment (p=0.0003), and prolonged the time to first moderate or severe exacerbation (p=0.0185) compared with placebo.

Figure 1. Change in mean pre-bronchodilator (A) and post-bronchodilator FEV1 (B) for roflumilast plus salmeterol or tiotropium

FEV1 = forced expiratory volume in 1 second
Adapted from reference 11.
Given that patients with COPD have different phenotypes, certain subgroups of patients may derive greater benefit from the anti-inflammatory action of roflumilast than others. A post-hoc pooled analysis of two 1-year studies (M2-111 and M2-112; n=2,686) determined that the subgroup of patients most likely to benefit from roflumilast were patients with chronic cough and sputum, as well as those with a history of exacerbations.

The rate of moderate-to-severe exacerbations was 14.3% lower with roflumilast compared with placebo (0.52 vs 0.61 exacerbations per year; p=0.026). A lower exacerbation rate was observed in specific subgroups of patients, including those with chronic bronchitis with or without emphysema (26.2% reduction; p=0.001), and those receiving inhaled corticosteroid treatment (18.8%; p=0.014). (Figure 2)

In patients with severe to very severe COPD receiving treatment with a LABA or a short-acting muscarinic antagonist, roflumilast reduced the rate of moderate-to-severe exacerbations by up to 21% (p=0.039) and prolonged the time to first and second exacerbations.

In clinical trials, roflumilast is generally well tolerated. Only mild and transient adverse events were typically reported. The most common adverse events occurring in ≥2% of patients were diarrhoea, weight loss and nasopharygitis. The weight loss observed with roflumilast mainly occurred within the first 6 months of treatment and was generally <3% of baseline weight.

Conclusion
As our understanding of the key role of inflammation in the pathophysiology of COPD becomes more clearly defined, therapies which specifically target this inflammatory component are likely to improve disease management. The oral once-daily PDE4 inhibitor roflumilast, the first in an emerging class of agents that targets inflammation, has demonstrated efficacy in improving lung function and reducing exacerbation rates. Available data support the use of roflumilast in patients with suboptimal disease control on other therapies. In addition, increasing evidence indicates that certain subgroups of patients will potentially derive the greatest benefit from targeted specific therapies such as roflumilast.

References:
13. Rennard SI, Calverley PMA, Goehring UM, Bredenbroeker D, Martinez FJ. Reduction of exacerbations by the PDE4 inhibitor roflumilast – the importance of defining different subsets of patients with COPD. Respir Res 2011;12:18.

“Patients most likely to benefit from roflumilast were those with chronic cough and sputum, as well as those with a history of exacerbations.”
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Joint leakage, osteoporosis, and diffuse bone lesions have been reported in patients receiving TNF blockers, including ENBREL. Patients should be monitored for the development of osteoporosis and other bone-related adverse events.

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Adverse Reactions: ENBREL is associated with an increased risk of serious infections, including tuberculosis. The risk of serious infections increases with the duration of therapy. ENBREL is also associated with an increased risk of osteoporosis and other bone-related adverse events. ENBREL is also associated with an increased risk of joint leakage, as the development of exacerbation of infection may occur. ENBREL is also associated with an increased risk of diffuse bone lesions, as the development of exacerbation of infection may occur.

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Introduction

Psoriatic arthritis (PsA) is an immune-mediated inflammatory arthritis associated with psoriasis that occurs in 0.3–1% of the population. Patients with PsA have heterogeneous clinical presentations with diverse articular and dermatological features as well as varied disease course and outcomes. There is increasing evidence suggesting that patients with PsA also have an increased risk of cardiovascular disease (CVD). We discuss the current literature indicating the relationship between PsA and cardiovascular risk.

Cardiovascular Morbidity and Mortality in PsA

Excess mortality in patients with PsA has been documented in several studies. In a mortality study of 428 patients with PsA, the standardized mortality ratio (SMR) for the female cohort was 1.59, and for the men, it was 1.65, indicating a 59% and 65% increase, respectively, in death rate compared with that of the general population. CVD was the leading cause of death, responsible for 36% of all causes. Cardiovascular mortality in PsA was 30% higher than in the general population. A recent mortality study in Hong Kong confirmed these findings. The age- and sex-adjusted SMR of PsA was 1.59, indicating a 59% increase in death rate compared with that of the general population in Hong Kong. CVD accounted for 20% of all causes of mortality.

Han et al investigated the prevalence of CVD in 3,066 patients with PsA. The standardized prevalence ratios (SPRs) of chronic heart failure, ischaemic heart disease, peripheral vascular disease and cerebrovascular disease were all significantly higher in patients with PsA than in healthy controls, indicating an increased risk of cardiovascular morbidity. The relative risk of coronary artery disease was 1.3 in patients with PsA, suggesting a 30% increase in risk. Patients with PsA also had increased prevalence of myocardial infarction and angina, with age- and sex-adjusted SPRs of 2.1 and 2.0, respectively. The prevalence of CVD in PsA (10%) resembled that of rheumatoid arthritis (RA) (12%). The age- and sex-adjusted odds ratio of CVD showed no significant difference between RA and PsA.

Subclinical CVD in PsA

Several studies investigated the prevalence of subclinical outcomes which precede cardiovascular events and mortality in PsA. Carotid intima-media thickness (IMT) of the common carotid artery, determined by ultrasonography, is a useful noninvasive surrogate marker of macrovascular atherosclerotic disease. IMT corresponds to the width of the vessel intima and media, which is the site of lipid deposition and plaque formation. Increased carotid IMT is a good indicator of generalized atherosclerosis and coronary artery disease, providing early information on atherosclerosis in subclinical stages. Several case-control studies have demonstrated that patients with PsA have a higher prevalence of subclinical artherosclerosis. The increase in carotid IMT in PsA was up to 23% compared with healthy controls. Patients with PsA without cardiovascular risk factors or clinically evident CVD still
had an 8.7% increase in carotid IMT, significantly higher than healthy controls.9 The prevalence of plaques, especially more severe plaque,8 in patients with PsA was also significantly increased.7

Endothelial dysfunction is considered an early feature in atherogenesis and has been consistently associated with cardiovascular risk factors.13 It encompasses an imbalance between vasodilating and vasoconstricting substances, leading to an impaired ability of the artery to dilate in response to physical and chemical stimuli.13 Post-occlusion flow-mediated vasodilatation (FMD%) of the brachial artery measured by ultrasonography is used to noninvasively evaluate endothelial function.14 In patients with PsA without cardiovascular risk factors or clinically evident CVD, FMD% was found to be significantly lower compared with healthy controls, indicating endothelial dysfunction in PsA as a potential basis for the association between PsA and atherosclerosis.15

Gonzalez-Juanatey et al did not find significant subclinical cardiac abnormalities in patients with PsA without cardiovascular risk factors or clinically evident CVD.16 However, Shang et al, using conventional echocardiography and tissue Doppler imaging, found that 65% of patients with PsA without established CVD had evidence of subclinical left ventricular dysfunction, a rate significantly higher than in healthy controls.17 Left ventricular dysfunction was more common in patients with cardiovascular risk factors than in those without.17

### Conventional and Unconventional Risk Factors of CVD in PsA

Patients with PsA have an increased prevalence of conventional cardiovascular risk factors.4,5,18-21 These risk factors contribute to not only overt but also subclinical CVD. The prevalence of hypertension, hyperlipidaemia, obesity and type 2 diabetes is higher in PsA patients than in the general population.4,5,8 Data on lipid profiles are slightly controversial. Jones et al found that high-density lipoprotein (HDL) cholesterol and its third subfraction, HDL3 cholesterol, were significantly reduced and the densest subfraction of low-density lipoprotein (LDL), LDL3, was significantly increased in patients with PsA.22 Lower levels of HDL cholesterol and its subfraction in PsA patients were also found by Skoczynska et al.23 A study by Tam et al, however, found that patients with PsA had higher HDL cholesterol levels, lower total cholesterol (TC) and LDL cholesterol levels, and a lower TC/HDL cholesterol ratio.18 A few studies have investigated the level of apolipoprotein A (apo-AI) and apolipoprotein B (apo-B). Tam et al found significant increases in serum apo-AI and apo-B levels in patients with PsA.18 However, Oliviero et al investigated apo-AI and TC in serum and synovial fluid in patients with PsA, and found no significant difference between patients and controls.24

The metabolic syndrome is a cluster of traditional risk factors that include abdominal obesity, atherogenic dyslipidaemia, hypertension, and insulin resistance. A recent study in Hong Kong found that the prevalence of the metabolic syndrome was significantly higher in PsA patients (38%) compared with matched controls (18%) or patients with RA (20%) or ankylosing spondylitis (AS) (11%).19 Patients with PsA were 2.44 times more likely to have the metabolic syndrome relative to patients with RA or AS.19

The increased cardiovascular risk in patients with PsA may be related to the inflammatory process. Inflammation participates centrally in all stages of the development of atherosclerosis, from the initial lesion to end-stage thrombotic complications.26 The increased levels of proinflammatory cytokines, which are characteristics of chronic inflammatory diseases such as PsA, can elicit a systemic inflammatory state that could, over time, promote atherosclerosis conducive to increased cardiovascular risk. C-reactive protein (CRP) is emerging as one of the predictors of CVD,26 and its levels also relate well with joint inflammation.27 Tam et al reported that low-grade inflammation as measured by high-sensitivity CRP was associated with obesity, hypertension, insulin resistance and dyslipidaemia in patients with PsA.18 The increased prevalence of obesity in PsA patients may also increase the burden of inflammation. Adipose tissue cells secret cytokines, chemokines, and hormone-like proteins which are involved in adipose tissue homeostasis, regulation of insulin sensitivity and metabolism, and also chronic inflammation.28 Adiponec tin has anti-inflammatory properties, and its levels were found to be reduced in patients with psoriasis.24 High levels of proinflammatory cytokines, such as tumour necrosis factor alpha (TNF-α), could downregulate the production of adiponectin and upregulate the production of leptin, which has a proinflammatory and proangiogenic role and can cause endothelial dysfunction in patients with inflammatory diseases.29

### Effects of Biologic Disease-modifying Antirheumatic Drugs in Risk of CVD in PsA

In a pilot study, Tam et al showed that 12-week anti-TNF-α therapy might be associated with significant reduction in IMT, along with improvement in clinical and laboratory manifestations in patients with PsA.30 The 2-year analysis showed that further regression of maximum IMT was possible only in patients who were continued on long-term anti-TNF-α therapy, suggesting that effective suppression of inflammation in patients with high-grade inflammation may potentially reverse early atherosclerotic lesions. Anti-TNF-α therapies were also shown to improve aortic stiffness and modify endothelial function in patients with inflammatory arthritis, including PsA.31,32 These findings support the pivotal role of inflammation in atherogenesis and the favourable effect of aggressive anti-inflammatory therapies on cardiovascular risk.

### Recommendations for Cardiovascular Risk Management

The European League Against Rheumatism has developed recommendations
for cardiovascular risk management in patients with RA and other inflammatory arthritis, including AS and PsA. Aggressive suppression of disease activity is necessary to lower cardiovascular risk. Annual assessment of cardiovascular risk using national guidelines is recommended for all patients with inflammatory arthritis. Any risk factors identified should be managed according to local guidelines. In the absence of local guidelines, cardiovascular risk management should follow the Systematic Coronary Risk Evaluation model, which is similar to the Framingham risk score. Statins, angiotensin-converting enzyme inhibitors, and/or angiotensin II blockers are preferred treatment options due to their potential anti-inflammatory effects.

Conclusion

PsA is associated with an increased prevalence of clinical and subclinical CVD due to accelerated atherosclerosis. In PsA, chronic inflammation acts independently and/or synergistically with traditional risk factors in the pathogenesis of atherosclerosis. Aggressive suppression of inflammation may prevent the progression of atherosclerosis and thus provide a favourable cardioprotective effect in patients with PsA.

References:

Journal Report – ADHD Medications Do not Increase Serious Cardiovascular Events in Adults

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A new study led by Dr Laurel Habel, PhD from the Kaiser Permanente Northern California, Oakland, USA reported no increase of serious CV events. This was a retrospective, population-based cohort study using electronic healthcare records from four different sites. The study included 443,196 adults aged 25–64 years, of whom 150,359 were users of ADHD medications at baseline. The drugs included methylphenidate, amphetamine, atomoxetine and pemoline. During 806,182 person-years of follow-up, 1,357 cases of myocardial infarction, 296 cases of sudden cardiac death and 575 cases of stroke were recorded. The multivariable-adjusted rate ratio of serious CV events for current users vs nonusers was 0.83 (95% confidence interval 0.72–0.96).

This study gives some reassurance to doctors who wish to prescribe psycho-stimulants to their adult ADHD patients. However, one must be aware that less serious problems like hypertension or cardiac arrhythmia are not addressed. Also, physicians need to continue to monitor CV status and complications in their patients.

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Management of Adverse Gastrointestinal Events in Patients on Antiplatelet Therapy, Part II: Gastrointestinal Bleeding Induced by Clopidogrel or Dual Antiplatelet Therapy

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Key words:
Clopidogrel (氯吡格雷), proton pump inhibitor (質子泵抑制劑), esomeprazole (埃索他拉唑), gastrointestinal bleeding (消化道出血)

Introduction

Clopidogrel was approved by the Food and Drug Administration for use in secondary prevention of heart attacks and stroke in 1997. The efficacy of clopidogrel added to aspirin has been established in patients with acute coronary syndrome (ACS) or myocardial infarction (MI), and percutaneous coronary stenting.1,2 However, the major complication is bleeding, particularly from the gastrointestinal (GI) tract.3

This review aims to examine the epidemiology and management of adverse upper GI events in patients receiving clopidogrel or dual antiplatelet therapy. Furthermore, the interaction between proton pump inhibitor (PPI) and clopidogrel will be reviewed.

Clopidogrel

Clopidogrel differs from aspirin in the mechanism by which it inhibits platelet aggregation.4 Clopidogrel inhibits platelet aggregation by irreversibly inhibiting the binding of adenosine diphosphate, a substance released from platelets during activation that amplifies the aggregation process. This agent does not impair prostaglandin-dependent mucosal protective and ulcer healing mechanisms, which is a side effect of aspirin.

Clopidogrel-induced Gastrointestinal Bleeding

In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, 19,185 patients were randomized to receive clopidogrel 75 mg/day or aspirin 325 mg/day.5 After a mean follow-up of 1.9 years, the incidence of severe adverse upper GI events was significantly lower for clopidogrel vs aspirin (dyspepsia, 0.97% vs 1.22%, p<0.05; severe GI bleeding [GIB], 0.52% vs 0.72%, p<0.05). Therefore, clopidogrel is safer than aspirin in average-risk patients.6

In high-risk patients with peptic ulcers, clopidogrel therapy alone is unsafe and PPI cotherapy is required. In a retrospective cohort study by Ng FH et al, the rate of ulcer bleeding induced by clopidogrel was 9% over 1 year in patients with previous peptic ulcers.6 History of overt upper GIB was a significant risk factor. Three randomized controlled studies showed similar findings. Ng FH et al compared the incidence of unhealed ulcers in patients receiving omeprazole plus either clopidogrel or aspirin.7 The treatment success rate for clopidogrel and aspirin was 94% and 95%, respectively. No GIB was observed in both groups.8 After ulcer healing and eradication of Helicobacter pylori (if infected), patients were randomized to receive either clopidogrel plus placebo or aspirin plus esomeprazole (20 mg twice daily) for 12 months. The cumulative incidence of recurrent bleeding was significantly higher in the clopidogrel group (8.6%) vs the aspirin plus esomeprazole group (0.7%). In Lai KC et al’s study, the design was similar to that of the second study except a smaller dose of esomeprazole (20 mg daily) was used.9 During a follow-up of 52 weeks, the cumulative incidence of recurrent ulcer complications was 0% in patients receiving esomeprazole and aspirin vs 13.6% in patients receiving clopidogrel. Therefore, aspirin plus esomeprazole is superior to clopidogrel alone in the secondary prevention of recurrent ulcer bleeding.

Gastrointestinal Bleeding Induced by Aspirin and Clopidogrel Cotherapy

The major adverse event of aspirin and clopidogrel (A+C) cotherapy is bleeding. In the Clopidogrel in Unstable Angina to Prevent Recurrent Ischaemic Events (CURE) study, which recruited patients with ACS, A+C cotherapy was associated with a significantly higher total number of bleeding complications (8.5%) vs aspirin monotherapy (5%).1 Excess major bleeding most frequently occurred in the GI tract. Major GIB occurred in
1.3% of patients treated with A+C co-therapy vs 0.7% of patients treated with aspirin alone (relative risk [RR]=1.79, 95% CI 1.25–2.66). In another study, patients with ischaemic stroke or transient ischaemic attacks were randomized to receive clopidogrel or A+C cotherapy. After a follow-up of 18 months, life-threatening bleeding was more common in the group receiving A+C cotherapy vs clopidogrel alone (2.6% vs 1.3%).

Gastrointestinal Bleeding

The adverse impact of bleeding in ACS or MI has been recognized recently. Patients with major bleeding had a 5-fold increase in mortality rate at 30 days (12.8% vs 2.5% in those without major bleeding; p=0.0001). However, minor bleeding also significantly increased the risk of death (adjusted RR=2.07, 95% CI 1.15–3.72). Therefore, prevention of GIB in patients with ACS is of paramount importance.

Preventing Gastrointestinal Bleeding During Aspirin and Clopidogrel Cotherapy

PPI therapy is highly effective in preventing upper GIB in patients with ACS or acute MI (AMI). Ng FH et al demonstrated that PPI therapy could significantly reduce the risk of upper GIB in patients receiving a combination of aspirin, clopidogrel and enoxaparin for ACS. The age-adjusted odds ratio (OR) for GIB was 0.068 (95% CI 0.010–0.272) for coprescription with a PPI. Moreover, a case-control study showed that PPI therapy is associated with reduced risk of upper GIB within 30 days of percutaneous coronary intervention (OR=0.08, 95% CI 0.02–0.40, p=0.002). In a retrospective study of patients receiving A+C cotherapy, the risk of major GIB was significantly lower in patients with coprescription of PPI than in those without (11.1% vs 1.8%, p=0.05). Recently, a large randomized controlled study demonstrated that omeprazole significantly reduces the incidence of the composite endpoint of upper GIB or symptomatic ulcer in patients receiving A+C cotherapy (hazard ratio [HR]=0.55, 95% CI 0.36–0.85, p=0.007). In a second randomized controlled study, the combination of esomeprazole (20 mg/day) and clopidogrel reduced the recurrence of endoscopic peptic ulcers compared with clopidogrel alone during the 6-month period (1.2% vs 11.0%, p=0.009). In conclusion, both esomeprazole and omeprazole are highly effective for prevention of GIB in patients on A+C cotherapy.

Proton Pump Inhibitor and Clopidogrel Interaction

Both clopidogrel and PPIs are prodrugs that require activation by the hepatic cytochrome P450 enzymes. This common pathway may lead to reduced conversion of clopidogrel to its active metabolite. The pharmacodynamic and clinical outcome studies are summarized below.

Pharmacodynamic Studies

A double-blind placebo-controlled trial has demonstrated that omeprazole significantly decreases clopidogrel’s inhibitory effect on platelet P2Y12. This is not a class effect, and this effect does not translate into adverse clinical outcome. A nonrandomized study found no significant difference in platelet reactivity among patients taking esomeprazole or pantoprazole and controls. In a randomized controlled study with peptic ulcer recurrence as a primary endpoint, a subgroup of 42 consecutive patients participated in a pharmacodynamic study. There were no differences in the percentages of aggregated platelets before and 28 days after esomeprazole therapy (31.0% ± 20.5% vs 30.1% ± 16.5%). Recently, our group has completed a larger double-blind randomized study that compared esomeprazole vs famotidine on the platelet inhibitory effect of clopidogrel. Eighty-eight patients on A+C cotherapy were randomized to receive esomeprazole 20 mg daily or famotidine 40 mg daily. The platelet reactivity unit on day 28 was 242.6 ± 89.7 and 237.5 ± 79.2 in the groups receiving esomeprazole and famotidine, respectively [mean difference=5.1, 95% CI -30.8 to 41.0, p=0.78]. In conclusion, esomeprazole does not reduce the platelet inhibitory effect of clopidogrel.

Clinical Outcome Studies

The result of clinical outcome studies remains controversial. Retrospective studies on the association between PPI use and major adverse cardiovascular events (MACE) demonstrated contradictory results. The unadjusted confounding factors may have a significant effect on results and their subsequent interpretation since PPI users were older, with more comorbidities and comedications. Two post-hoc analyses of previous large-scale randomized controlled studies demonstrated that PPI use is not associated with an increase in MACE. Furthermore, a large randomized controlled study of 3,873 patients receiving clopidogrel suggested that treatment with omeprazole does not increase the risk of MACE vs placebo, although the sample size might be underpowered due to premature termination for financial reasons. MACE occurred in 4.9% and 5.7% of patients on omeprazole and placebo, respectively (HR=0.99, 95% CI 0.68–1.44).

Conclusion

The addition of clopidogrel to aspirin has been established in patients with ACS, AMI and percutaneous coronary stenting. However, the major complication is GIB, which is associated with MACE. PPIs including omeprazole and esomeprazole are highly effective in preventing GIB. Pharmacodynamic studies demonstrated that omeprazole decreases clopidogrel’s inhibitory effect on platelet P2Y12. This is not a class effect. Esomeprazole does not reduce the platelet inhibitory effect of clopidogrel. Furthermore, post-hoc analyses of previous large-scale randomized controlled studies and a prospective randomized controlled study suggest that PPI therapy does not increase MACE.

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References:
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Management of Adverse Gastrointestinal Events in Patients on Antiplatelet Therapy, Part II: Gastrointestinal Bleeding Induced by Clopidogrel or Dual Antiplatelet Therapy

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